Remarks

Claims 1-38 are in the application. Claims 17-25 and 31-38 have been withdrawn from consideration by the Examiner, and have been canceled herein. Claims 1-10, 12-16 and 26-30 have been rejected and claim 11 has been objected to. Claims 1, 5, 6 and 13 have been amended herein.

The Examiner has required restriction of the claims to one of three inventions, as explained in the office action. Applicants confirm their election of Group I, claims 1-15 drawn to compounds, and further, claims 26-30 drawn to the use of the Group I compounds for treating stroke. Claims 17-25 and 31-38, drawn to non-elected subject matter, have been canceled herein, but Applicants reserve the right to pursue the subject matter of these claims in one or more divisional or continuation applications.

The Examiner has objected to the specification on the basis that the identification of the second provisional parent application is missing in paragraph 1 of the specification, and has required correction. Applicants respectfully direct the Examiner's attention to the Preliminary Amendment filed February 23, 2001 in which the required correction was made. Therefore, Applicants deem this objection moot and respectfully request its withdrawal.

Claims 5, 6, and 13 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner notes that: claim 5 contains a typographical error; claims 5, 6 and 13 appear to be incomplete; and claim 13 claims a compound outside the scope of its parent claim. The typographical error has been corrected by amendment to claim 5 herein. These claims are not, in fact, incomplete, but the claimed compounds are outside the scope of claim 1. Applicants originally made these claims dependent on claim 1 by mistake, but claims 5, 6 and 13 have now been made independent via amendment herein. These claims cover certain novel intermediate compounds which are used to make the compounds of claim 1, as set forth in the specification. Claims 5, 6 and 13 are believed to meet the requirements of 35 U.S.C. § 112, second paragraph; therefore, Applicants respectfully urge withdrawal of the instant rejection.

Claims 1, 2, 16 and 26-30 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in an enabling manner. Specifically, the Examiner has pointed to the scope of the definitions of R^1, R^2 and R^3. In view of the amendments to claim 1 made herein, this rejection is deemed moot. Applicants believe that claims 1, 2, 16, and 26-30 meet all the requirements of 35 U.S.C. § 112 and urge withdrawal of this rejection.

Claims 1-10 and 12-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over

Abou-Gharbia (5,254,552) in view of Cliffe (5,420,278). The Examiner has stated that Abou-Gharbia ('552) teaches similar compounds for uses associated with 5HT1A serotonin receptor site binding, and that Cliffe ('278) teaches, for similar compounds and uses, the placement of benzyl groups on an alkyl carbon adjacent to the nitrogen of a carboxamide group. On this basis, the Examiner has concluded that it would have been obvious that one could replace H with benzyl on the N in the carboxamide group in the '552 compounds and obtain the claimed compounds with the expectation that these compounds would have the claimed uses. Applicants traverse the rejection for the reasons set forth below.

Abou-Gharbia '552 describes compounds which differ structurally from those claimed by Applicants. All of the reference compounds lack the Applicants' YR_1 group. Additional differences from the claimed compounds include: the alkyl chain between the piperazine and the carboxamide group may be 2-5 carbon atoms long; the group on the other side of the carboxamide group may vary considerably in both the alkyl and cyclic portions thereof; and, the N of the carboxamide may be substituted, which is not permitted in Applicants' compounds. By selecting the "right" choice for each of these variables, using the Applicants' invention as a guide, the Examiner has identified compounds that differ from some of Applicants' compounds by virtue of lacking the YR_1 group. Nevertheless, even these compounds are not compounds of the claimed invention, as the Examiner has conceded. This reference clearly does not teach or suggest the claimed invention.

Cliffe '278 describes piperazine compounds which differ from some of the claimed compounds at least in that the adamantyl or noradamantyl group is replaced by a different group. However, the most preferred reference compounds (see reference column 2, lines 52-64) are those wherein an ethyl chain is attached to a $-CO_2R^6$ ester group or a $-CONR^5R^9$ amide group, whereas in the claimed compounds the ethyl is attached to an -NCO-(nor)adamantyl group. Furthermore, in the preferred reference compounds the NR^5R^9 group forms a cyclic compound that includes the N, rather than having a separate cyclic group attached to the amide group. Therefore, not only is there no (nor)adamantyl group in the reference compounds, but the reference teaches that the preferred compounds do not have the same atoms, or the same arrangement of atoms in the central chain as do the presently claimed compounds. Using the Applicants' invention as a guide, the Examiner has selected those (non-preferred) reference compounds which are closest to the claimed compounds, which the Examiner has admitted are not compounds claimed by Applicants. This reference clearly does not teach or suggest the claimed invention.

Having used Applicants' invention as a guide to select those compounds within the broad genus of each reference which are closest to Applicants' claimed compounds, the Examiner concluded that it would have been obvious to replace the alpha hydrogen on the compounds of Abou-Gharbia '552 with the benzyl group taught by Cliffe '278 to obtain the instant invention, with the expectation that the compounds would have the properties claimed by Applicants. The Examiner has chosen not to enlighten us at to why this particular substitution would be obvious to make, rather than some other substitution, for example, replacing the adamantyl of the '552 patent with the preferred group from the '278 patent.

Applicants respectfully submit that the Examiner has engaged in a classic exercise of hindsight reasoning. At every step in the Examiner's analysis, Applicants invention has been used as a guide to select the "right" pieces with which to assemble the invention. The Examiner has failed to explain, or even hint, at where in the references one skilled in the art would find the motivation or guidance to make all the "right" choices for each genus, and further to combine the reference teachings to make the one substitution in the compounds of the '552 patent that would produce the Applicants' invention. Logically, one would assume that one considering the '278 patent would look toward the preferred compounds described therein, rather than the compounds closest to the present invention. However, with the Applicants' teaching as a guide the Examiner set out to reconstruct the invention from prior art, and that provided the necessary guidance to make all the "right" choices. This guidance, however, does not exist in the prior art. Consequently, Applicants respectfully submit that the present invention would not have been obvious to those skilled in the art at the time the invention was made, absent knowledge of the present invention.

An additional and separate reason that Applicants' invention would not have been obvious to one skilled in the art who did not have the benefit of Applicants' teaching, is that the skilled practitioner could not predict that the claimed compounds would function as they do. The present invention comprises compounds that have agonist or partial agonist activity and thus are useful for treating neurodegeneration; no such use or activity is found in the cited references. At best, even using the Examiner's hindsight analysis to obtain the compounds, it may have been obvious to try these compounds for some of the claimed uses (but not for treating neurodegeneration); that is not a sufficient basis for an obviousness rejection.

A further separate basis for finding that the invention is not obvious is that the prior art does not teach one how to make the compounds of the present invention. To make the invention obvious, the prior art must contain sufficient teachings to enable one skilled in the art to make the invention.

Compounds which have different structures require different starting materials and, even when the structures seem very similar, an entirely different synthesis route may be needed. Therefore, the method for making the structurally different compounds must be clear from the prior art. The Examiner has not shown that to be the case here. If the Examiner believes that the method of making the claimed compounds is obvious form the cited art, Applicants' respectfully request that the Examiner explain where in the cited art the requisite teaching is found.

For all the foregoing reasons, Applicants find that the cited references, whether taken individually or in combination, do not teach or suggest the claimed invention, and Applicants respectfully request withdrawal of the rejection of claims 1-10 and 12-16 under 35 U.S.C. § 103(a).

Claim 11 has been objected to as being dependent on a rejected claim, but has been deemed to cover patentable subject matter, and would be allowed if rewritten in independent form. Applicants thank the Examiner for noting that his claim covers patentable subject matter. However, in view of the foregoing arguments and amendments, Applicants believe that claim 11 is dependent on a patentable claim and does not need to be rewritten in independent form. Therefore, this objection is deemed moot.

In view of the amendments and arguments made herein, Applicants believe that all of claims 1-16 and 26-30 are patentable and respectfully solicit the allowance of these claims at an early date. The Examiner is invited to call the undersigned attorney at her convenience should she find that such action would be likely to expedite the allowance of this application.

No fees are believed to be due herewith; however, if a fee is required it may be charged to Deposit Acct. No. 01-1425.

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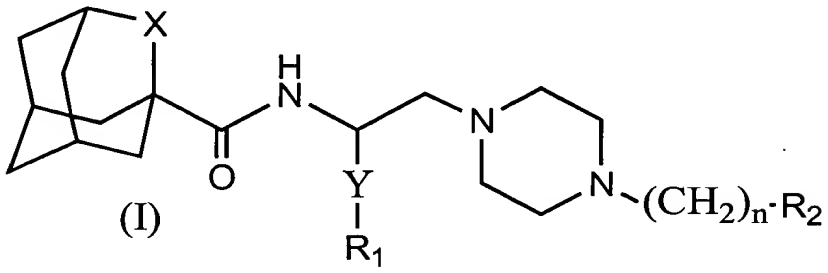
Version With Markings To Show Changes Made

1. A compound of the formula (I):



(I)

wherein:

X is selected from $-CH_2-$ or a chemical bond;

Y is selected from $-(CH_2)_m-$ or $-(CH_2)-O-(CH_2)-$;

m is selected from the integer 0 or 1;

n is selected from the integer 0 or 1;

R_1 and R_2 are independently selected from the group consisting of aryl, [or] monocyclic heteroaryl [of from] having 5 – [10]6 ring atoms of which 1-3 ring atoms are independently selected from the group consisting of N, S and O, and bicyclic heteroaryl having a phenyl ring fused to a monocyclic heteroaryl ring as defined above, optionally substituted with F, Cl, Br, I, -OH, $-NH_2$, $-CO_2H$, $-CO_2-C_1-C_6$ alkyl, -CN, $-NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perhaloalkyl, OR_3, or C_1-C_6 perhaloalkoxy;

R_3 is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, [mono or bicyclic heteroaryl] monocyclic heteroaryl having 5 –6 ring atoms of which 1-3 ring atoms are independently selected from the group consisting of N, S and O, and bicyclic heteroaryl having a phenyl ring fused to a monocyclic heteroaryl ring as defined above, C_7-C_{14} aralkyl, and mono or bicyclic heteroaralkyl consisting of a C_1-C_4 alkyl having a substituent which is a mono or bicyclic heteroaryl as defined above, where the aryl or heteroaryl group is optionally substituted with one to three substituents independently selected from the group consisting of F, Cl, Br, I, CN, $-NH_2$, $-NO_2$, -OH, alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perhaloalkyl, C_1-C_6 alkoxy, and C_1-C_6 perhaloalkoxy; and

the optical isomers or a pharmaceutically acceptable salt thereof.

5. [A] The compound [of Claim 1 which is] (R)-Phenylalanine-N-[4-(phenylmethyl)-1-piper[i]azinyl]carboxamide Dihydrochloride.

6. [A] The compound [of Claim 1 which is] (R)-[1-(Phenylmethyl)-2-[(4-phenylmethyl)-1-piperazinyl]ethyl]amine.

13. [A] The compound [of Claim 1 which is] (R)-[1-(Phenylmethyl)-2-[4-(2-methoxyphenyl)-1-piperazinyl]-2-oxo-ethyl]-carbamic acid tert-butyl ester.